REVIEW ARTICLE

Allergic reactions to vaccines

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To cite this article: Wood RA. Allergic reactions to vaccines. *Pediatr Allergy Immunol* 2013: **00**.

Keywords
anaphylaxis; hypersensitivity; immunization; vaccines

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Accepted for publication 6 June 2013

DOI:10.1111/pai.12102

Anaphylactic reactions to vaccines are rare but do occur, and have been reported for nearly every vaccine. And while the reaction rate per each dose of vaccine is low, this is a common clinical question due in large part to the enormous numbers of vaccines administered. Reactions are most often due to vaccine constituents rather than the microbial components of the vaccine, but in many instances, the specific ingredient triggering the reaction cannot be definitively identified. Evaluation of patients with suspected vaccine reactions should begin by determining whether the symptoms and timing of the reaction were consistent with a true allergic reaction, followed by an assessment to determine whether the patient needs further doses of the vaccine in question, or similar vaccines, in the future. Skin and serologic testing to vaccines and vaccine constituents can then be performed to further assess the potential cause of the reaction and to develop a plan for future immunizations. Specific guidelines for the administration of influenza vaccines to egg allergic patients have been revised to allow virtually all patients to receive this vaccine in a straightforward manner.

Concerns about possible allergic reactions to immunizations are frequently raised by both patients/parents and primary care providers. Estimates of true allergic, or immediate hypersensitivity, reactions to routine vaccines range from 1 per 50,000 doses for DTP to about one per 500,000–1,000,000 doses for most other vaccines (1). In a large study from New Zealand, data were collected over a 5-yr period on 15 marketed vaccines, revealing an estimated rate of one immediate hypersensitivity reaction per 450,000 doses of vaccine administered (2). Another large study, conducted within the Vaccine Safety Datalink (VSD), described a range of reaction rates to over 7.5 million doses. Depending on the study design and the time after the immunization event, reaction rates varied from 0.65 cases/million doses (95% confidence interval: 0.21–1.53) to 1.53 cases/million doses (95% CI of 0.04–8.52) when additional allergy codes were included (3). For some vaccines, particularly if allergens such as gelatin are part of the formulation (such as Japanese encephalitis), higher rates of serious allergic reactions may occur (4). Although these per dose estimates suggest that true hypersensitivity reactions are quite rare, the large number of doses that are administered, especially for the commonly used vaccines, makes this a relatively common clinical problem.

Etiology and clinical manifestations

Vaccines, like all other drugs, have the potential to cause allergic reactions. As detailed below, vaccine components that may be allergenic include the infectious agent or specific antigen(s), preservatives, stabilizers, and residual media used in preparation of the vaccine, as well as inadvertent contaminants introduced during vaccine handling. Individual vaccine components that have been implicated in acute vaccine reactions include egg protein, gelatin, yeast, and a variety of other additives (5).

The clinical manifestations of possible vaccine reactions are best classified based on the specific symptoms reported and the timing of the appearance of symptoms (6). In general, reactions can be classified as immediate or delayed, which helps to distinguish IgE-mediated reactions from those that do not involve IgE. This is important as IgE-mediated reactions carry the risk of life-threatening anaphylaxis if the patient is reexposed to the same vaccine. Immediate, IgE-mediated allergic reactions to vaccines are typical of reactions to other allergens and may involve the skin, including flushing, itching, urticaria, and angioedema, the respiratory track, including nasal congestion, a sensation of throat closure or choking, stridor, cough, wheeze, and dyspnea, and/or the cardiovascular system, including faintness, syncope, altered mental status, palpitations, and hypotension.

Delayed reactions can appear hours to days after vaccine administration and are unlikely to be IgE-mediated. Several types of delayed reactions to vaccines have been noted, including common reactions like fever or local swelling, and a variety of less common reactions, which may be immunologic

or non-immunologic in nature. Reactions such as fever and local reactions are very common, generally self-limited, and are not usually contraindications to receive future doses of the same vaccine (7). Less common delayed immunologic reactions include serum sickness, polyarthritis, and erythema nodosa, which occasionally may be considered a contraindication for future doses of the same vaccine (8–10). The remainder of this review will focus on immediate-type adverse reactions that are most likely to be IgE-mediated.

Specific vaccine constituents causing allergic reactions

A variety of vaccine components have been implicated as causes of allergic reactions, including anaphylaxis. These include gelatin, egg protein, milk protein, chicken, preservatives, antimicrobial agents, yeast, and natural rubber latex, as well as the vaccine antigen itself. Several internet sites provide lists of potential allergens in vaccines, including the Institute for Vaccine Safety (www.vaccinesafety.edu) as well as the CDC (www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf.

Gelatin is a common vaccine component that is likely the most frequent cause of allergic reactions to measles, mumps, and rubella (MMR), varicella, and Japanese encephalitis vaccines (11–14), as well as a less common cause of reactions to influenza vaccine (15). Patients with such reactions may also report a history of allergy to the ingestion of gelatin and gelatin-containing foods, although the absence of such a history – including the lack of reactions to foods high in gelatin content – is common and does not rule out the possibility of an allergic reaction to a gelatin-containing vaccine.

Egg protein is present in yellow fever, influenza, measles/mumps/rubella, and some rabies vaccines, although the amounts are likely to only be clinically significant only in the yellow fever vaccine (16). A history of allergy after the ingestion of egg should therefore be sought prior to the administration of yellow fever vaccine, and persons with positive histories should be evaluated by an allergist. MMR and rabies vaccines can be administered in patients with egg allergy without additional testing, and recommendations regarding the administration of influenza vaccines to persons allergic to egg are detailed below. Chicken proteins may also be present in yellow fever vaccine and may be responsible for reactions in chicken allergic recipients (17).

Casein, a cow's milk protein, has recently been implicated as a potential cause of anaphylaxis to diphtheria, tetanus, and pertussis vaccines (DTaP or Tdap) in a small number of children with severe milk allergy (18). These vaccines are prepared in a medium derived from cow's milk protein, and trace amounts of residual casein have been demonstrated in these preparations. However, it is important to recognize that the vast majority of patients with even severe milk allergy tolerate these vaccines without difficulty, so no changes to vaccine recommendations have resulted from these case reports (19).

Vaccines commonly contain preservatives such as thimerosal, aluminum, and phenoxyethanol. These preservatives have not been documented to cause immediate-type allergic reactions, but may cause delayed-type hypersensitivity reactions. They may also cause contact dermatitis when applied topically to the skin, although this is not a contraindication to receive vaccines containing these products. Aluminum-containing vaccines may rarely cause persistent nodules at the injection site, possibly because of delayed hypersensitivity or other immune responses to aluminum.

Antimicrobial agents are also often added in trace amounts to vaccines, most commonly neomycin, polymyxin B, and streptomycin. While there are no confirmed reports that these agents have caused anaphylactic reactions to vaccines, patients who have experienced allergic reactions to these antibiotics should be evaluated by an allergy specialist prior to the administration of vaccines containing them. However, contact dermatitis to these antimicrobials is not a contraindication to administration of vaccines containing these agents.

Latex is another allergen implicated in vaccine reactions, as the materials used in vaccine vial stoppers and syringe plungers frequently contain latex. While such reactions are uncommon, this may occasionally pose a risk to latex-allergic patients, especially if multidose vials are used (20, 21). The latex content of vaccine packaging can be found at www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf. If a patient with latex allergy needs to receive a vaccine that is only available with a latex stopper, the stopper should be removed and the vaccine drawn up directly from the vial without passing the needle through the stopper.

Yeast is a component of Hepatitis B and human papillomavirus vaccines and while potentially allergenic, reactions due to yeast in vaccines appear to be very rare (22). However, if a patient has a clear clinical history of allergy to yeast, it would be appropriate to skin test with yeast-containing vaccines prior to administration.

A variety of constituents have therefore been implicated as the causes of allergic reactions to vaccines. However, it is important to recognize for many reactions – even those with severe anaphylaxis – no specific vaccine component can be definitively identified as the cause of the reaction. Many patients may therefore be reacting to the actual antigen, or infectious agent, contained in the vaccine (23–28). These reactions will be harder to characterize, but the same approach to revaccination that is detailed below will apply.

Approach to patients with suspected vaccine allergy

Several excellent practice parameters and guidelines have been published describing the clinical management of patients with suspected vaccine allergy (29–31). Some of these recommendations, such as the management of influenza vaccine in patients with egg allergy, may frequently change so the reader is encouraged to access the most up to date information whenever possible, such as from the Centers for Disease Control (www.cdc.gov/vaccines). It is also important to recognize that questions about vaccine allergy may result from two general concerns, each of which may require a different approach individualized to that patient. The first relates to patients who have had a possible reaction prior to vaccination, while the second relates to patients with a known allergy – such

as egg allergy – that might put them at risk for specific immunizations.

For the patient with a history of a possible reaction to a prior immunization, the specific approach needs to carefully consider several key questions:

1 Was the reported reaction consistent with an IgE-mediated allergy with regard to the signs, symptoms, and timing? For example, the patient with a history of urticaria, angioedema, and respiratory distress occurring five minutes after vaccine administration is very different from the patient experiencing a non-specific rash 24 h after the vaccine was given.
2 Has the patient experienced suspected reactions to any prior vaccines? If so, this might help to focus the evaluation on specific vaccine constituents that are common among the vaccines suspected of causing reactions.
3 Will the patient need additional doses of this vaccine or other vaccines with common constituents? If the patient will never need additional doses of the vaccine, no evaluation may be needed, although it is important to also consider whether their reaction puts them at higher risk for future issues with other vaccines or foods, in which case a thorough evaluation may be needed even if no further doses of the suspect vaccine are required.

With these questions in mind, each patient can then be approached individually using a combination of clinical assessment, laboratory testing, and cautious re-administration of necessary immunizations.

Clinical assessment

With regard to clinical assessment, the clinician should first decide whether future doses of the vaccine are truly needed. Some vaccines may be considered less important than others, for example immunization against a potentially fatal illness (e.g., measles) compared to an illness that is less likely to pose life-threatening risks (e.g., influenza). In addition, as many vaccines are given as a series, some patients may mount protective responses, sometimes even long lasting, to fewer than the recommended number of doses. For some immunizations, it may therefore be a reasonable option to measure and monitor antibody titers to assess the level of protection and the need for future doses, recognizing that antibody levels are not a useful measure of protection for all vaccines and that immunity might wane over time.

Allergy testing with vaccines and vaccine constituents

If it is determined that additional doses of a vaccine should be administered, skin testing with the vaccine and/or vaccine constituents should be performed. This process may be relatively simple if only a single vaccine was administered or for more complicated if multiple vaccines were given at the same visit, which is certainly the norm for the typical pediatric encounter.

A number of approaches to vaccine skin testing have been suggested, but current guidelines recommend that testing be initiated with a skin prick test to the full-strength vaccine, unless the patient has a history of a very severe reaction in which case it is appropriate to dilute the vaccine 1:10 or even 1:100 to initiate skin prick test (30, 31). If the prick skin test is negative, an intradermal test with the vaccine diluted 1:100 should then be performed. All tests need to be interpreted carefully with appropriate positive and negative controls, recognizing that falsely positive skin test results may occur. These may be the result of true but clinically irrelevant IgE responses or to irritant effects of the vaccine. In one prior study, we found that irritant reactions were common at concentrations of 1:10 or undiluted vaccines, especially with influenza, MMR, and varicella vaccines (32). At the 1:100 concentration, rates of irritant reactions were far less common with the most frequent being 5% for DT and DTaP and 15% for influenza. Delayed responses to vaccine skin tests are common, most likely representing prior immunity, and should not raise concern in the evaluation of IgE-mediated vaccine allergy.

If the suspected vaccine contains specific constituents known to be allergenic, testing should also be conducted for those components. These primarily include egg (for reactions to yellow fever or influenza vaccines), gelatin (see Table 1 for the gelatin content of specific vaccines), latex, and yeast. Skin test reagents for egg and yeast are commercially available. Skin prick test solutions for gelatin can be prepared by dissolving one teaspoon of gelatin powder in 5 ml of normal saline. Skin test extracts for latex are commercially available in many countries but not in the United States. In addition to skin testing, *in vitro* testing for allergen-specific IgE is available in most commercial laboratories for egg, gelatin, latex, and yeast. For gelatin, it is important that assays for both porcine and bovine products be conducted.

Examples of skin and serologic testing that would be appropriate in the evaluation of suspected reactions to specific vaccines are presented in Table 2.

Administration of vaccines to patients with a history of prior reactions

If skin and *in vitro* testing is negative, especially if the intradermal skin test to the vaccine is negative, the chance

Table 1 Gelatin content of common vaccines

Influenza (Fluzone, Sanofi Pasteur)	250 μg per 0.5 ml dose
Influenza (FluMist, Medimmune Vaccines)	2000 μg per 0.2 ml dose
Measles, Mumps, Rubella (ATTENUVAX, MERUVAXII, MMRII, MMVAX, MUMPSVAX, Merck)	14,500 μg per 0.5 ml dose
Measles, Mumps, Rubella, Varicella (ProQuad, Merck)	11,000 μg per 0.5 ml dose
Rabies (RabAvert, Chiron)	12,000 μg per 1.0 ml dose
Varicella (VARIVAX, Oka/Merck)	12,500 μg per 0.5 ml dose
Yellow Fever (YF-VAX, Sanofi Pasteur)	7500 μg per 0.5 ml dose
Zoster (Zostavax, Oka/Merck)	15,580 μg per 0.65 ml dose

This information may change with subsequent vaccine development so please check the package insert for specific information.

Table 2 Examples of testing used to assess specific vaccines suspected of causing allergic reactions

Vaccine	Skin testing	*In vitro* IgE testing
DtaP	DTaP, DT, Tetanus toxoid, Gelatin	Gelatin
Hepatitis B	Hepatitis B, Yeast	Yeast
Influenza	Influenza, Egg, Gelatin	Egg, Gelatin
MMR	MMR, Measles, Mumps, Rubella, Gelatin, Egg	Egg, Gelatin
Varicella or Zoster	Varicella, Gelatin	Gelatin
Yellow fever	Yellow fever, Egg, Gelatin	Egg, Gelatin

Whenever possible, the same vaccine from the same manufacturer that was given at the time of the reaction should be used for testing.

that the patient has a true allergy to the vaccine or to any vaccine constituent is very small. The usual dose of the vaccine can therefore be administered under observation in a facility where epinephrine and other treatments are readily available, preferably with at least a 30-min observation period after vaccination.

If skin or *in vitro* testing to the vaccine or a vaccine component is positive, alternative approaches to vaccination should be considered (33). However, if the vaccine is considered necessary – that is, the benefit of the vaccine clearly outweighs the potential risk of vaccine administration – it is usually possible to still safely administer the vaccine using a graded dose protocol (33–35). These decisions should be carefully considered on a case by case basis, recognizing that even administration using a graded dose protocol still carries the risk of anaphylaxis. This should be conducted with informed consent and only in a setting prepared to treat severe allergic reactions should one occur.

Administration of vaccines to patients allergic to a vaccine component

As noted, in addition to the patient with a history of a suspected vaccine reaction, many patients with a known allergy to a vaccine component will present with concerns regarding their potential for risk upon receipt of such vaccines. This most commonly occurs with regard to influenza vaccination in patients with egg allergy, although patients may also present with a history of allergy to gelatin or other vaccine constituents that could pose risk with the administration of other specific vaccines.

The administration of influenza vaccine to patients with egg allergy is a common clinical issue, and thankfully one that has become less complicated over the past few years, due to both an expanding body of evidence regarding overall safety and the fact that influenza vaccines have been produced with more consistently low egg allergen content. Currently, most of the available inactivated influenza vaccines, as well as the intranasal live-attenuated influenza vaccine, are cultured on fluid from chicken embryos and do contain small amounts of egg protein. On balance, however, it is also important to recognize that many of the same patients with egg allergy are also those at higher risk of an adverse outcome from influenza infection, including younger children and those with asthma, for whom influenza vaccine should be provided if at all possible.

A number of studies have now consistently shown that anaphylaxis to influenza vaccine is rare, even in patients with a history of severe reactions to egg (36–45). In addition, most vaccine manufacturers now provide the egg protein content of their influenza vaccines, and all current vaccines are reported to contain ≤1 μg per 0.5 ml dose. Further reassurance has been provided by independent studies that have demonstrated even lower egg protein content of many vaccines than that reported by the manufacturer (46–48).

Another positive development has been the production of influenza vaccines that do not contain egg proteins. An inactivated vaccine (Optaflu) produced using cultured mammalian cells was approved for use in adults in the European Union, Iceland, and Norway in 2007. This same vaccine (called Flucelvax) was approved by the US Food and Drug Administration in November 2012 for individuals ≥18 yr of age (49, 50). Most recently, a second trivalent egg-free influenza vaccine (FluBlok) was approved by the FDA in January 2013 for patients aged 18–49 yr (51).

Therefore, for adults with egg allergy, egg-free influenza vaccines are now an option and should be used if available. However, if not available or not indicated for age, influenza vaccines can be safely provided to the vast majority of patients with egg allergy. In the past, it was recommended that patients with egg allergy undergo skin testing with the actual vaccine and/or divided dosing to ensure safety. However, neither of these procedures are currently recommended as they did not lead to any reduction in adverse reactions, especially given the fact that adverse reactions occur so rarely in any circumstance (31, 52–55).

Although slight variations exist among the current recommendations – and it is likely that guidelines will change further over the next few years – the overall recommendations for influenza vaccination in patients with egg allergy are as follows:

1 Patients with a history of egg allergy who are currently ingesting egg may receive the vaccine in the usual manner.
2 Patients with a history of reactions no more severe than hives after egg ingestion can receive influenza vaccine in a primary care provider's office, provided the appropriate personnel and equipment are available.
3 Patients with a history of more severe reactions to egg, or who are sensitized to egg but have had no known exposures to egg, should receive their vaccine in an allergy specialist's office.
4 Although the intranasal vaccine contains low amounts of egg protein, it should not be used in egg allergic patients as there is little data on its safety.

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